REMARKS

Claims 1-9 were previously cancelled. Claims 10-20 were previously added. Accordingly, Claims 10-20 are pending. Accompanying this Amendment is an unexecuted Declaration under 37 C.F.R. § 1.132. An executed declaration will follow shortly.

Rejection under 35 U.S.C. 102(e) (U.S.P.N. 6,028,099)

Claims 10-17 and 19-20 have been rejected as being anticipated by U.S. Patent No. 6,028,099 ("the '099 patent") in view of the Cole Eye Institute article. (See Office Action page 2, paragraph 3.)

Independent Claim 10 recites methods of treating retinal edema, macular edema and cystoid macular edema by administering an octreotide. Independent Claim 14 recites methods of treating these ocular disorders by *topically* administering a somatostatin analog in the form of an ophthalmic liquid preparation.

In contrast, the '099 patent discloses treating choroidal neovascularization (CNV) with the administration of an inhibitor of the protein tyrosine kinase pathway. (See col. 2, lines 15-18.) The Examiner points to the section of the patent which lists "various compounds that can be co-administered" with the inhibitor. Within this extensive list of compounds, the somatostatin analog SMS 201-995 is enumerated. (See col. 9, lines 14-24.)

The '099 patent was filed on March 13, 1998 and issued on February 22, 2000. The parent application of the present continuation application is U.S. Serial No. 09/258,240, filed on February 26, 1999. Thus, the parent application was filed before the '099 patent issued.

A 37 CFR § 1.131 Declaration executed by Dr. Robertus Wilhelmus Kuijpers was filed on April 25, 2005. Two 37 CFR § 1.131 Declarations executed by the other two inventors (*i.e.*, Dr. Petrus Martinus van Hagen and Dr. Goitzen Seerp Baarsma) were filed on

December 28, 2005. The January 24, 2006 Advisory Action states that these two declarations were not entered. Applicants request entry of these two declarations.

The three aforementioned 1.131 Declarations establish that conception of the present invention was achieved *prior to* the filing date of the '099 patent. Accordingly, the '099 patent is **not** available as a reference against the present application.

In particular, as can be seen in the declarations at paragraphs 3 and 4, the inventors treated a patient suffering from an ocular disorder associated with edema with a somatostatin analog on October 16, 1996. As can be seen in the declarations at paragraphs 5 and 6, subsequent to October 16, 1996, there was a continuous diligence in reducing the invention to practice.

Since the present invention antedates the '099 patent, the '099 patent cannot be cited as a prior art reference. Accordingly the anticipation rejection is obviated.

However, even if the '099 patent could be cited (which Applicants strongly refute), the instant anticipation rejection of independent Claim 20 can be overcome for other reasons. Claim 20 recites methods of treating ocular disorders by "administering a pharmaceutical composition that **consists essentially of** octreotide..." The addition of an inhibitor of the protein tyrosine kinase pathway to a pharmaceutical composition that "consists essentially of" octreotide would materially affect the basic and novel characteristics of the pharmaceutical composition. For example, it is well known in the art that tyrosine kinase inhibitors have significant side effects. Thus, octreotide *without* a kinase inhibitor provides a safer clinical profile than octreotide *with* a kinase inhibitor.

It is *always* a principal goal in clinical medicine that side effects of medical treatments be minimized. The combination of octreotide with a drug with significant side effects would lead to a higher risk of side effects than when octreotide is used alone. Moreover, in the specification, it is shown that side effects were monitored and evaluated. See page 14, line

18, and page 15, line 26-27, of the specification. Thus, a minimization of side effects were *specifically* contemplated by the invention. Accordingly, excluding an agent which is known to have substantial side effects, such as the kinase inhibitors, was contemplated. The "consisting essentially of" language excludes such agents.

To demonstrate the previous assertion, a 37 U.S.C. § 1.132 declaration accompanies the present amendment. The declaration demonstrates that it is well known in the art that tyrosine kinase inhibitors have significant side effects.

In particular, Dr. Kuijpers states "**Somatostatin analogues** have been used for more than 15 years and have been **proven to be safe drugs**." In contrast, he states that "Tyrosine kinase inhibitors are not yet on the market, or only recently introduced on the market. Tyrosine kinase inhibitors have been described with a significant pattern of side-effect." (See paragraphs 7 and 8 of the Declaration.)

Dr. Kuijpers also recognizes that, as with virtually all drugs, "that when one uses two active compounds together (instead of just one active compound) more side-effects may occur." Accordingly, Dr. Kuijpers concludes that "a somatostatin analogue administered *without* a kinase inhibitor provides a safer clinical profile than a somatostatin analogue administered *with* a kinase inhibitor." (See paragraphs 9 and 10 of the Declaration.)

Accordingly, the accompanying 37 U.S.C. § 1.132 Declaration clearly demonstrates that the addition of a second active ingredient, a protein tyrosine kinase inhibitor, to a pharmaceutical composition that "consists essentially of" a somatostatin analogue would materially affect the basic and novel characteristics of the pharmaceutical composition. For example, the addition of a tyrosine kinase inhibitor would potentially lead to various adverse effects thereby being a much less attractive drug product than the instantly claimed product. Thus, the claimed invention is not anticipated by the '099 patent.

As further evidence, Exhibit I is enclosed. Exhibit I is a drug information sheet for a tyrosine kinase inhibitor. At the section bridging pages 2 and 3, entitled "Adverse Reactions Significant," numerous side effects are given. Further, starting at the bottom of page 3 in the section entitled "Drug Interactions," a list is given of side effects due to interactions with various drugs. Thus, a combination of a somatostatin analog with a drug with significant side effects would lead to a higher risk of side effects than when the somatostatin analog is used alone.

Moreover, **the Examiner has accepted the assertion that the addition of an inhibitor of the protein tyrosine kinase pathway** to a pharmaceutical composition that "consists essentially of" a somatostatin analogue **would materially affect the basic and novel characteristics** of the pharmaceutical composition in the counterpart application (U.S.S.N. 09/519,647). Accordingly, the same assertion should be accepted in the present application.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 18 recites a method of topically treating diabetic retinopathy with the administration of an octreotide in the form of an ophthalmic liquid preparation. The Examiner maintains the rejection of Claim 18 as not providing enablement for topical eye administration. (See Office Action page 3, paragraph 5.) The Examiner cites U.S. Patent No. 6,669,950 (hereinafter "the '950 patent") as discussing "problems associated with administering drugs to the posterior of the eye..."

In the accompanying 37 U.S.C. § 1.132 declaration, Dr. Kuijpers states that "Topical administration of a somatostatin analogue is effective in treating the aforementioned ocular disorders [i.e., retinal edema, macular edema, cystoid macular edema, age related macular degeneration, diabetic retinopathy, and central serous chorio-retinopathy]." (See paragraphs 12 and 13 of the Declaration.) Further experimental results demonstrating such efficacy will follow.

Moreover, in the April 1, 2005 Amendment, references were provided which demonstrate that topical compositions have been successfully used to treat posterior eye ailments, *e.g.*, glaucoma. In the present Office Action, the Examiner responds that "glaucoma [is] not a posterior eye disease."

The Applicants respectfully point out that the **'950 patent** (*i.e.*, the Examiner's cited reference) lists **glaucoma as a posterior eye ailment** at col. 1, line 23. (Note, Applicants have previously pointed out that the '950 patent lists glaucoma as a posterior eye ailment on page 6, last paragraph, of the April 1, 2005 Amendment.)

Additionally, according to M.PE.P. § 2164.04:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (Emphasis added.)

The instant specification teaches and describes the subject matter of Claim 18, *i.e.*, the treatment of diabetic retinopathy by the topical administration of octreotide. Thus, Claim 18 complies with the enablement requirement. Also, working examples are not necessary to comply with the enablement requirement. (See M.PE.P. § 2164.02.)

The '950 patent speaks only about disadvantages of periocular injections of a specific drug type, *i.e.*, angiogenesis inhibitors, not about periocular injections of all drug types. The patent does not speak of periocular injections in general. (See col. 1, lines 52-55, of the '950 patent.) It is improper to expand the teaching of the '950 patent to drugs other than angiogenesis inhibitors. In particular, the '950 patent does not teach anything about octreotide.

Furthermore, as stated above, topical compositions have been successfully used to treat posterior eye ailments, *e.g.*, glaucoma. By way of example, Exhibits 1-5 were attached to the April 1, 2005 Amendment. Those exhibits are articles and a package insert demonstrating the use of several topically applied drugs to treat glaucoma. Thus, Applicants have provided evidence to demonstrate that drugs applied topically are used to treat posterior eye ailments.

Since the subject matter of Claim 18 complies with 35 U.S.C. 112, first paragraph, Applicants respectfully request withdrawal of the enablement rejection.

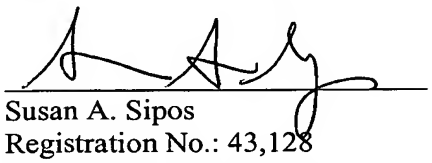
Obvious Type Double Patenting Rejection under 35 U.S.C. §101

The Examiner has also provisionally rejected the Claims 10-17 and 19-20 under the judicially created doctrine of obvious type double patenting in view of copending Application Serial No. 09/519,647. (See Office Action page 4, paragraph 7.)

Application Serial No. 09/519,647 has not yet been allowed. Once such application is allowed, Applicants will consider filing a terminal disclaimer which would ensure that the patent term of any patent that may issue from the present application would not extend beyond the term of any patent issued from Application Serial No. 09/519,647.

Applicants respectfully submit that the application, including Claims 10-20, is now in condition for allowance, which action is earnestly solicited. **The Examiner assured the Applicants that he would *not* issue a first Office Action until he speaks with the Applicants in order to place the claims into an allowable form.** Applicants' undersigned attorney await the Examiner's comments.

Respectfully submitted,



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Gleevec (Imatinib): Drug Information

(For additional information see "Gleevec (imatinib): Patient drug information")

U.S. BRAND NAMES — Gleevec®

PHARMACOLOGIC CATEGORY
Antineoplastic Agent, Tyrosine Kinase Inhibitor

DOSING: ADULTS
CML:
Chronic phase: Oral: 400 mg once daily; may be increased to 600 mg daily in the event of disease progression, loss of previously achieved response, or failure to achieve response after at least 3 months of therapy and in the absence of severe adverse reaction
Accelerated phase or blast crisis: 600 mg once daily; may be increased to 800 mg daily (400 mg twice daily) in the event of disease progression, loss of previously achieved response, or failure to achieve response after at least 3 months of therapy and in the absence of severe adverse reaction

Gastrointestinal stromal tumors: 400-600 mg/day.

Note: Dosage should be increased by at least 50% when used concurrently with a potent enzyme-inducing agent (ie, rifampin, phenytoin).

Dosage adjustment for hepatotoxicity or other nonhematologic adverse reactions: Refer to "Hepatic Impairment" dosing.

Dosage adjustment for hematologic adverse reactions:
Chronic phase (initial dose 400 mg/day in adults or 260 mg/m2/day in children) or GIST (initial dose 400 mg or 600 mg): If ANC <1.0 x 109/L and/or platelets <50 x 109/L: Discontinue until ANC ≥1.5 x 109/L and platelets ≥75 x 109/L; resume treatment at original initial dose of 400 or 600 mg/day (260 mg/m2/day in children). If depression in neutrophils or platelets recurs, withhold until recovery, and re-institute treatment at a reduced dose:
Children:
If initial dose 260 mg/m2/day, reduce dose to 200 mg/m2/day
If initial dose 340 mg/m2/day, reduce dose to 260 mg/m2/day
Adults:
If initial dose 400 mg, reduce dose to 300 mg
If initial dose 600 mg, reduce dose to 400 mg
Accelerated phase or blast crisis: Adults: Check to establish whether cytopenia is related to leukemia (bone marrow aspirate). If unrelated to leukemia, reduce dose of imatinib by 25%. If cytopenia persists for an additional 2 weeks, further reduce dose to 50% of original dose. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop treatment until ANC ≥1.0 x 109/L and platelets ≥20 x 109/L, resume treatment at 50% of original dose.

DOSING: PEDIATRIC

CML (chronic phase): Oral: 260 mg/m2/day; may be increased to 340 mg/m2/day in the event of disease progression, loss of previously achieved response, or failure to achieve response after at least 3 months of therapy and in the absence of severe adverse reaction. Dose may be given once daily or in 2 divided doses.

Note: Dosage should be increased by at least 50% when used concurrently with a potent enzyme-inducing agent (ie, rifampin, phenytoin).

Dosage adjustment for hepatotoxicity or other nonhematologic adverse reactions: Refer to "Hepatic Impairment" dosing.

Dosage adjustment for hematologic adverse reactions: Refer to adult dosing.

DOSING: ELDERLY — Refer to adult dosing.

DOSING: HEPATIC IMPAIRMENT — Hepatotoxicity or other nonhematologic adverse reactions: If elevations of bilirubin >3 times upper limit of normal (ULN) or transaminases (ALT/AST) >5 times ULN occur, withhold until bilirubin <1.5 times ULN or transaminases <2.5 times ULN. Resume treatment at a reduced dose:

Children:
If initial dose 260 mg/m2/day, reduce dose to 200 mg/m2/day
If initial dose 340 mg/m2/day, reduce dose to 260 mg/m2/day

Adults:
If initial dose 400 mg, reduce dose to 300 mg
If initial dose 600 mg, reduce dose to 400 mg

DOSAGE FORMS — Tablet: 100 mg, 400 mg

GENERIC EQUIVALENT AVAILABLE — No

ADMINISTRATION — Should be administered with food and a large glass of water. Tablets may be dispersed in water or apple juice, stir until dissolved and use immediately.

USE — Treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML), including newly-diagnosed patients as well as patients in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; treatment of pediatric patients with Ph+ CML (chronic phase) recurring following stem cell transplant or who are resistant to interferon-alpha therapy; treatment of Kit-positive (CD117) unresectable and/or (metastatic) malignant gastrointestinal stromal tumors (GIST)

ADVERSE REACTIONS SIGNIFICANT — Adverse reactions listed were established in patients with a wide variation in level of illness or specific diagnosis. In many cases, other medications were used concurrently (relationship to imatinib not specific). Effects reported in children were similar to adults, except that musculoskeletal pain was less frequent and peripheral edema was not reported.

>10%:
Central nervous system: Fatigue (29% to 41%), pyrexia (5% to 41%), headache (25% to 35%), dizziness (11% to 13%), insomnia (10% to 13%)
Dermatologic: Rash (26% to 44%), pruritus (8% to 13%), bruising (2% to 11%)
Endocrine & metabolic: Fluid retention (3% to 22% includes aggravated edema, anasarca, ascites, pericardial effusion, pleural effusion, pulmonary edema, excludes GIST); hypokalemia (5% to 13%)
Gastrointestinal: Nausea (42% to 71%), diarrhea (30% to 60%), vomiting (15% to 56%), abdominal pain (23% to 37%), weight increased (3% to 30%), dyspepsia (11% to 24), flatulence (16% to 23%), anorexia (6% to 17%), constipation (6% to 15%), taste disturbance (1% to 14%)
Hematologic: Hemorrhage (18% to 52%), neutropenia (grade 3 or 4: 2% to 48%),

thrombocytopenia (grade 3 or 4: <1% to 31%)
Neuromuscular & skeletal: Muscle cramps (27% to 55%), musculoskeletal pain (11% to 46%), arthralgia (25% to 36%), joint pain (27%), myalgia (8% to 25%), weakness (5% to 12%), back pain (10% to 11%), rigors (8% to 11%)
Ocular: Lacrimation (6% to 11%)
Respiratory: Cough (12% to 26%), dyspnea (9% to 20%), nasopharyngitis (8% to 19%), upper respiratory tract infection (3% to 15%), pharyngolaryngeal pain (14%), epistaxis (5% to 13%), pneumonia (3% to 12%), sore throat (8% to 11%)
Miscellaneous: Superficial edema (53% to 76%), night sweats (10% to 14%)

1% to 10%:
Central nervous system: Paresthesia (1% to 10%)
Hematologic: Anemia (grade 3 or 4: <1% to 4%)
Hepatic: Ascites or pleural effusion (GIST: 4% to 6%), alkaline phosphatase increased (grade 3 or 4: <1% to 5%), ALT increased (grade 3 or 4: <1% to 4%), bilirubin increased (grade 3 or 4: <1% to 4%), AST increased (grade 3 or 4: <1% to 3%)
Renal: Albumin decreased (grade 3 or 4: 3% to 4%), creatine increased (grade 3 or 4: <1% to 3%)
Miscellaneous: Flu-like syndrome (<1% to 10%)

<1% (Limited to important or life-threatening): Acute generalized exanthematous pustulosis, angioedema, aplastic anemia, bullous eruption, cardiac failure, cerebral edema, embolism, erythema multiforme, exfoliative dermatitis, glaucoma, ileus, intestinal obstruction, intracranial pressure increased, interstitial pneumonitis, pancytopenia, papilledema, pancreatitis, paresthesia, pericarditis, photosensitivity, pulmonary fibrosis, seizure, Stevens-Johnson syndrome, thrombosis, vitreous hemorrhage

CONTRAINDICATIONS — Hypersensitivity to imatinib or any component of the formulation; pregnancy

WARNINGS / PRECAUTIONS — Often associated with fluid retention, weight gain, and edema (probability increases with higher doses and age >65 years); occasionally leading to significant complications, including pleural effusion, pericardial effusion, pulmonary edema, and ascites. Use caution in patients where fluid accumulation may be poorly tolerated, such as in cardiovascular disease (CHF or hypertension) and pulmonary disease. Severe dermatologic reactions have been reported; reintroduction has been attempted following resolution. Successful resumption at a lower dose (with corticosteroids and/or antihistamine) has been described; however, some patients may experience recurrent reactions.

Use with caution in renal impairment, hematologic impairment, or hepatic disease. May cause GI irritation, hepatotoxicity, or hematologic toxicity (neutropenia or thrombocytopenia). Median duration of neutropenia is 2-3 weeks; median duration of thrombocytopenia is 3-4 weeks. Hepatotoxic reactions may be severe. Has been associated with development of opportunistic infections. Use with caution in patients receiving concurrent therapy with drugs which alter cytochrome P450 activity or require metabolism by these isoenzymes. Safety and efficacy in patients <3 years of age have not been established. Long-term safety data is limited.

DRUG INTERACTIONS — Substrate of CYP1A2 (minor), 2D6 (minor), 2C8/9 (minor), 2C19 (minor), 3A4 (major), Inhibits CYP2C8/9 (weak), 2D6 (weak), 3A4 (strong)

(For additional information: Launch Lexi-Interact™ Drug Interactions Program)

Note: Drug interaction data are limited. Few clinical studies have been conducted. Many interactions listed below are derived by extrapolation from in vitro inhibition of cytochrome P450 isoenzymes.

Acetaminophen: Chronic use may increase potential for hepatotoxic reaction with imatinib (case report of hepatic failure with concurrent therapy).

Benzodiazepines: Imatinib may inhibit the metabolism of alprazolam, diazepam, and triazolam resulting in elevated serum concentrations; monitor for increased sedation and psychomotor impairment

Beta-blockers: Imatinib may inhibit the metabolism of metoprolol and propranolol resulting in cardiac toxicity; monitor for bradycardia, hypotension, and heart failure if combination is used; not established for all beta-blockers (unlikely with atenolol or nadolol due to renal elimination)

Carbamazepine: Imatinib may inhibit the metabolism of carbamazepine resulting in increased carbamazepine concentrations and toxicity; monitor for altered carbamazepine response

Carvedilol: Imatinib may inhibit the metabolism of carvedilol; monitor carefully for increased carvedilol effect (hypotension and bradycardia)

Cisapride: Imatinib may inhibit the metabolism of cisapride, potentially leading to malignant arrhythmias; avoid concurrent use

Clozapine: Imatinib may inhibit the metabolism of clozapine; monitor

CYP3A4 inducers: CYP3A4 inducers may decrease the levels/effects of imatinib. Example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycins. Dosage of imatinib should be increased by at least 50% (with careful monitoring) when used concurrently with a strong inducer.

CYP3A4 inhibitors: May increase the levels/effects of imatinib. Example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, and verapamil.

CYP3A4 substrates: Imatinib may increase the levels/effects of CYP3A4 substrates. Example substrates include benzodiazepines, calcium channel blockers, mirtazapine, nateglinide, nefazodone, tacrolimus, and venlafaxine. Selected benzodiazepines (midazolam and triazolam), cisapride, ergot alkaloids, selected HMG-CoA reductase inhibitors (lovastatin and simvastatin), and pimozide are generally contraindicated with strong CYP3A4 inhibitors.

Dextromethorphan: Imatinib may inhibit the metabolism of dextromethorphan; monitor

Haloperidol: Imatinib may inhibit the metabolism of haloperidol and cause extrapyramidal symptoms (EPS); monitor patients for EPS if combination is used

HMG-CoA reductase inhibitors (except pravastatin and fluvastatin): Imatinib may inhibit the metabolism of HMG-CoA reductase inhibitors. The risk of myopathy/rhabdomyolysis may be increased. Switch to pravastatin/fluvastatin or monitor for development of myopathy.

Immunosuppressants (cyclosporine, sirolimus, and tacrolimus): Imatinib may inhibit the metabolism of immunosuppressants; monitor serum concentrations and renal function

Ketoconazole (and itraconazole, possibly fluconazole): May inhibit metabolism of imatinib; potential for toxicity may be increased

Macrolide antibiotics (erythromycin and clarithromycin): May inhibit the metabolism of imatinib, potentially increasing toxicity.

Methadone: Imatinib may inhibit the metabolism of methadone; monitor for increased effect

Nefazodone: Imatinib may inhibit the metabolism of nefazodone; monitor

Phenothiazines: Imatinib may inhibit the metabolism of phenothiazines; concurrent use of

agents associated with QT prolongation (thioridazine, mesoridazine) should be avoided

Phenytoin: Imatinib may inhibit the metabolism of phenytoin and may increase phenytoin levels; phenytoin decreases serum concentrations of imatinib

Pimozide: Imatinib may inhibit metabolism of pimozide; concurrent use should be avoided

Propafenone: Imatinib may inhibit the metabolism of propafenone; toxicity may be increased; avoid concurrent administration

Protease inhibitors (indinavir, saquinavir, ritonavir): May decrease metabolism of imatinib; monitor

Quinidine: Imatinib may inhibit the metabolism of quinidine; toxicity may be increased; avoid concurrent administration

Sibutramine: Imatinib may inhibit the metabolism of sibutramine; avoid concurrent administration

Sildenafil, tadalafil, vardenafil: Serum concentrations may be increased. Specific dosage adjustment guidelines not established. Recommendations for other strong CYP3A4 inhibitors include single sildenafil doses not to exceed 25 mg in 48 hours, a single tadalafil dose of 10 mg in 72 hours, or a single vardenafil dose not to exceed 2.5 mg in 24 hours.

SSRIs (fluoxetine, sertraline): Imatinib may inhibit the metabolism of SSRIs; monitor. Some SSRIs may inhibit metabolism of imatinib via CYP3A4, increasing its serum concentrations and potential toxicity.

Tramadol: Imatinib may decrease metabolism of tramadol; monitor

Trazodone: Imatinib may inhibit the metabolism of trazodone resulting in increased toxicity; monitor

Tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline): Imatinib may inhibit the metabolism of tricyclic antidepressants resulting is elevated serum concentrations; monitor

Vinca alkaloids (vincristine, vinblastine): Imatinib may inhibit the metabolism of vinca alkaloids; toxicity may be increased; avoid concurrent administration

Warfarin: Imatinib may decrease metabolism of warfarin, increasing the hypoprothrombinemic response; monitor INR closely

ETHANOL / NUTRITION / HERB INTERACTIONS
Ethanol: Avoid ethanol.

Food: Food may reduce gastrointestinal irritation.

Herb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease imatinib plasma concentration).

PREGNANCY RISK FACTOR — D (show table)

PREGNANCY IMPLICATIONS — There are no adequate and well-controlled studies in pregnant women. Has been noted to be teratogenic in animal models. Women of childbearing potential are advised not to become pregnant.

LACTATION — Excretion in breast milk unknown/not recommended

DIETARY CONSIDERATIONS — Should be taken with food and a large glass of water to decrease gastrointestinal irritation.

PRICING — (data from drugstore.com)
Capsules (Gleevec)
100 mg (30): $534.99

Tablets (Gleevec)
100 mg (30): $575.99
400 mg (30): $2181.99

MONITORING PARAMETERS — CBC (weekly for first month, biweekly for second month, then periodically thereafter), liver function tests (at baseline and monthly or as clinically indicated), renal function, weight, and edema/fluid status.

TOXICOLOGY / OVERDOSE COMPREHENSIVE — Experience with overdose is limited (>800 mg/day). Hematologic adverse effects are more common at dosages >750 mg/day. Treatment is symptomatic and supportive.

CANADIAN BRAND NAMES — Gleevec®

INTERNATIONAL BRAND NAMES — Gleevec® (AR, CA, GT, JO, JP, KR, MX, PE, PR, SY); Glivec® (AT, CH, CO, CZ, DE, DK, EC, FI, FR, GB, HR, HU, ID, IT, NO, PL, PT, RO, SG, SI, TH, YU)

MECHANISM OF ACTION — Inhibits Bcr-Abl tyrosine kinase, the constitutive abnormal gene product of the Philadelphia chromosome in chronic myeloid leukemia (CML). Inhibition of this enzyme blocks proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as in fresh leukemic cells in Philadelphia chromosome positive CML. Also inhibits tyrosine kinase for platelet-derived growth factor (PDGF), stem cell factor (SCF), c-kit, and events mediated by PDGF and SCF.

PHARMACODYNAMICS / KINETICS
Protein binding: 95% to albumin and alpha1-acid glycoprotein

Metabolism: Hepatic via CYP3A4 (minor metabolism via CYP1A2, CYP2D6, CYP2C9, CYP2C19); primary metabolite (active): N-demethylated piperazine derivative

Bioavailability: 98%

Half-life elimination: Parent drug: 18 hours; N-demethyl metabolite: 40 hours

Time to peak: 2-4 hours

Excretion: Feces (68% primarily as metabolites, 20% as unchanged drug); urine (13% primarily as metabolites, 5% as unchanged drug)
Clearance: Highly variable; Mean: 8-14 L/hour (for 50 kg and 100 kg male, respectively)

PATIENT EDUCATION — Take exactly as directed; do not alter or discontinue dose without consulting prescriber. Take with food and a large glass of water. Avoid alcohol, chronic use of acetaminophen or aspirin, OTC or prescription medications, or herbal products unless approved by prescriber. Maintain adequate hydration (2-3 L/day) unless instructed to restrict fluids. You will be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds or contagious persons, and do not receive any vaccination unless approved by prescriber). You may experience headache or fatigue (use

caution when driving or engaged in tasks requiring alertness until response to drug in known); loss of appetite, nausea, vomiting, or mouth sores (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased dietary fiber and fluids, exercise may help); or diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea). Report chest pain, palpitations, or swelling of extremities; cough, difficulty breathing, or wheezing; weight gain greater than 5 lb; skin rash; muscle or bone pain, tremors, or cramping; persistent fatigue or weakness; easy bruising or unusual bleeding (eg, tarry stools, blood in vomitus, stool, urine, or mouth); persistent gastrointestinal problems or pain; or other adverse effects.

(For additional information see "Gleevec (imatinib): Patient drug information")

REFERENCES

1. Brunstein, CG, McGlave, PB. The Biology and Treatment of Chronic Myelogenous Leukemia. Oncology 2001; 15:23.

2. Druker, BJ, Sawyers, CL, Kantarjian, H, et al. Activity of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in the Blast Crisis of Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia With the Philadelphia Chromosome. N Engl J Med 2001; 344:1038.

3. Druker, BJ, Talpaz, M, Resta, DJ, et al. Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia. N Engl J Med 2001; 344:1031.

4. Hehlmann, R, Hochhaus, A, Berger, U, et al. Current Trends in the Management of Chronic Myelogenous Leukemia. Ann Hematol 2000; 79:345.

5. Joensuu, H, Roberts, PJ, Sarlomo-Rikala, M, et al. Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient With a Metastatic Gastrointestinal Stromal Tumor. N Engl J Med 2001; 344:1052.

6. Kantarjian, H, Sawyers, C, Hochhaus, A, et al. Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia. N Engl J Med 2002; 346:645.

GRAPHICS

FDA Use-in-Pregnancy Ratings for Drugs

Category	Interpretation
A	**Controlled studies show no risk** – Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	**No evidence of risk in humans** – Either animal findings show risk (but human findings do not), or, if no adequate human studies have been done, animal findings are negative.
C	**Risk cannot be ruled out** – Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
D	**Positive evidence of risk** – Investigational or postmarketing data show risk to the fetus. However, potential benefits may outweigh the risk.
X	**Contraindicated in pregnancy** – Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient.